MANAV RACHNA INTERNATIONAL UNIVERSITY

Short Synopsis

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Title: A COMPUTATIONAL STUDY OF DIABETES MELLITUS

DEPARTMENT OF MATHEMATICS

FACULTY OF ENGINEERING & TECHNOLOGY

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ABSTRACT

Mathematical Biosciences includes the study of the application of mathematical modeling and mathematical techniques to get an insight into the problems of Biosciences. In a mathematical model broad computational resources are required to analyze the complex system behavior not only through the analytic solution but experimenting the model by adjusting the parameters of the system and then observing the differences in the results of the experimented mathematical model .One of the most complicated and crucial physiological control systems in humans is the glucose-Insulin regulatory system. Under the consideration of real life parameters new mathematical models of glucose-insulin regulatory system have been proposed with the help of differential equations. The biological hormonal effects, causing the Glucose homeostasis in human body for regulation of glucose-insulin levels in normal values, are considered as parameters in these models. The validations of these models are possible through the available clinical data and previously experimented models.

Keywords: Mathematical model, diabetes mellitus, glucose-insulin, differential equations, Biomathematics

CONTENTS

S. No.	Description	Page No.
1	Introduction	1
2	Literature Review	2-3
3	Description of Broad Area	3-5
4	Objective of the Study	5
5	Methodology to be adopted	5-8
6	Expected outcome of the research	8-9
7	Proposed Time Frame	9
8	References	9-12

1. Introduction

Biomathematics is an interdisciplinary subject with a vast exponentially growing literature which is scattered over different disciplines. A large number of mathematical models have been developed to get an insight into complex biological, ecological and physiological situations. A variety of mathematical techniques have been employed to solve these models. These include techniques for solution of differential, difference, integral, delay-differential and integro-differential equations as well as techniques of linear, non-linear, dynamic and stochastic programming, calculus of variations and so on. In this field we are not just restricted for using only existing mathematical model but we can evolve new mathematical methods for dealing with the existing complicated situations of life sciences. Since the situation in life sciences are quite complex, we should have an insight into a situation before formulating the new mathematical model. In mathematical modeling formulate the model and its consequences can be deduced by using mathematical techniques and the result can be compared with the observations. The discrepancies between the hypothetical conclusion and observations will lead to the further improvement. Because of irregular lifestyle of people now a day the incidence of diabetes is increasing rapidly. Diabetes mellitus is the disease of millions and if the projections are right, a quarter billion people across the globe will be diabetic by the year 2025. As per the data collected for all age groups the incidence of diabetes mellitus worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The diabetic population in the world is expected to rise from 171 million in 2000 to 366 million in 2030. India ranked number one as the country with the highest number of diabetes patients in 1995, at 31.7 million in 2000, with a projected 57.2 million in 2025, and 79.4 million in 2030. According to the study of SITE (Screening India's Twin Epidemic) 62% of the diabetic patients in Delhi having uncontrolled Diabetes and rest are having controlled Diabetes. This report is generated by Aventis Pharma Limited (Sanofi-Aventis Group (2010)).

A differential equation based mathematical model will be proposed in our research work and MATLAB will be used to solve the mathematical problems. The main focus is to present a mathematical model for Diabetic patients and their treatment on the basis of recent developments in medical sciences.

2. Literature Review

WHO (1999)“ report discussed about Diabetes mellitus which includes its classifications, types, symptoms, urination, how it can be diagnosed, amount of glucose in blood and many other ways how to treat the diabetes. This is the report given by the WHO expert committee.

Sarah Wild et.al. (2004) studied how to approximate the incidence of diabetes and the number of diabetic people of all ages for years 2000 and 2030. As per the data collected for all age groups the incidence of diabetes mellitus worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The incidence of diabetes is higher in men than women, but as per the record there are more diabetic women as compared to men. These findings indicate that the “diabetes occurrence” will continue even if levels of obesity remain constant.

Boutayeb et.al (2004) applied ordinary differential equations and numerical techniques which are used to analyze the population size of diabetes with complication and without complications. The model shows the approach to obtain efficient and cost-effective strategies by acting on diabetes incidence and/or controlling the evolution to the stage of complications.

Boutayeb et.al (2006) studied about the population size of diabetics. The study also reveals the number of patients with complications. By suitable definition of a parameter, the mathematical model may be described as a linear or a non-linear one. For the stability condition the non-linear case is discussed and the critical values of the population are studied.

Athena Makroglou et.al. (2006) had given an overview of different mathematical models is given which shows the relation of glucose-insulin regulatory system to the Diabetes and it was enhanced with the survey on available software. The mathematical model consists of Ordinary differential, Partial Differential, Delay differential and integro-differential equations.

S.O.Adewale et.al. (2007) defined a mathematical model used for study of diabetes mellitus and hence concluded the impact of different levels of physicals activities on the steadiness of the disease. They observed that when we exercise the hazard of becoming diabetics reduces.

Emma Geraghty (2008) in the project explained the importance of Delay differential equations is explained with many different applications, particularly in the biological and medical worlds. It gives the further idea for insulin therapy by using the solution of the differential equations.

Yesenia Cruz Rosado et.al. (2009) presented a new model based on a non-homogeneous ordinary differential equations which is 3x3 system. To determine the coefficient parameters of

the system based on actual data from GTT he used a non linear least square method .With the help of simulations an indicator was also provided similar to the one which was proposed by E. Ackerman (1969), to diagnose the condition of diabetic. Additionally, they developed a graphical user interface to facilitate the patient's data entering and the visualization of the results.

Sh. Yasini et.al. (2009) developed a new model which shows the regulations of the blood glucose level of diabetic patient (Type1) under an intensive insulin treatment. To maintain the normoglycemic average of 80mg/dl and the normal condition for free plasma insulin concentration in severe initial state reinforcement learning theory was used with the help of closed-loop control scheme expert knowledge. By using Q-learning algorithm an offline insulin delivery rate was obtained without requiring a model of the environment dynamics. To evaluate the effectiveness of the proposed model and to check its superiority in controlling hyperglycemia over other existing algorithms Computer simulations were used .

3. Description of Broad Area / Topic

The models will be developed in pharmacokinetics which deals with the distribution of the drugs, chemicals, tracers or radioactive substances among various compartment of the body. Compartments are the real or fictitious part of the body. Examples are: blood circulatory system, intestinal tract, tissues, cells, blood plasma, heart etc.

Diabetes mellitus can be defined as a disease in glucose-insulin regulatory system resulting from defects in insulin secretion or insulin action or both. In 1980 World Health Organization (WHO) considered two classifications of Diabetes Mellitus and named it as IDDM (Insulin Dependent Diabetes Mellitus or Type1) and NIDDM (Non Insulin Dependent Diabetes Mellitus or Type2).

Type1 diabetes mellitus results from the body's failure to produce insulin, and currently requires the person to inject insulin or wear an insulin pump. This form was previously referred to as "insulin-dependent diabetes mellitus"(IDDM) or "juvenile diabetes". Type2 diabetes mellitus results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. This form was previously referred to as “non insulin-dependent diabetes mellitus” (NIDDM).The third main form, Gestational diabetes, occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level. It may precede development of type2 diabetes mellitus. Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion.

Diabetes is associated with a large number of abnormalities in insulin metabolism, ranging from an absolute deficiency to a combination of deficiency and resistance, causing an inability to dispose glucose from the blood stream. The three factors are responsible: Insulin sensitivity, Glucose effectiveness, and pancreatic responsiveness. Common symptoms of diabetes are lethargy from marked hyperglycemia, hypoglycemia, polyuria, polydipsia, blurred vision, weight loss and susceptibility to certain infections Untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include disease, chronic, and diabetic retinopathy (retinal damage). Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as stopping smoking and maintaining a healthy body weight.

The requirements for diagnostic confirmation for a person presenting with severe symptoms and gross hyperglycemia differ from those for the asymptomatic person with blood glucose values found to be just above the diagnostic cut–off value. Severe hyperglycemia detected under conditions of acute infective, traumatic, circulatory or other stress may be transitory and should not in itself be regarded as diagnostic of diabetes. The diagnosis of diabetes in an asymptomatic subject should *never* be made on the basis of a single abnormal blood glucose value.

For the asymptomatic person, at least one additional plasma/blood glucose test result with a value in the diabetic range is essential, either fasting, from a random (casual) sample, or from the oral glucose tolerance test (OGTT). If such samples fail to confirm the diagnosis of diabetes mellitus, it will usually be advisable to maintain surveillance with periodic re–testing until the diagnostic situation becomes clear. In these circumstances, the clinician should take into consideration such additional factors as ethnicity, family history, age, adiposity, and concomitant disorders, before deciding on a diagnostic or therapeutic course of action. An alternative to blood glucose estimation or the OGTT has long been sought to simplify the diagnosis of diabetes.

Glycated hemoglobin, reflecting average glycaemia over a period of weeks, was thought to provide such a test. Although in certain cases it gives equal or almost equal sensitivity and specificity to glucose measurement, it is not available in many parts of the world and is not well enough standardized for its use to be recommended at this time. Diabetes in children usually presents with severe symptoms, very high blood glucose levels, marked glycosuria, and ketonuria.

In recent years, mathematical modeling of developmental processes has earned new respect. Not only have mathematical models been used to validate hypotheses made from experimental data, but designing and testing these models has led to testable experimental predictions.

4. Objectives of the Study / Problem Identification

1. To study the application of some mathematical model in diabetes mellitus using differential equations to get an insight into the problem in this area.
2. To review some major developments in modeling of diabetes mellitus that have taken place.
3. To analyze the parameters of different types of diabetic patients which will helpful in creating a feasible model.
4. To create models whose results will be helpful in clinical treatment of diabetes mellitus as this disease is not only limited to the people having age more than 40 or 45 but its level is also spreading into the children and adolescents.

5. Methodology to be adopted

In this research work we use:

- Computer techniques which include Matlab and Mathematica to solve the equations developed by modeling
- Classical mathematical techniques which include Ordinary Differential equation, Partial Differential equations, Integro-differential equations, Delay Differential equations.

(i) Ordinary differential equations - A differential equation which contains functions of only one independent variable, and one or more of their derivatives with respect to that variable.

Example:

$$\frac{dG}{dt} = -m_1 G - m_2 I + g(t), \quad \frac{dI}{dt} = -m_3 I - m_4 G + i(t),$$

(ii) Partial Differential Equations - partial differential equations (PDE) are a type of differential equations i.e. a relation involving an unknown function (or functions) of several independent variables and their partial derivatives with respect to those variables.

PDEs are used to formulate, and thus aid the solution of problems involving functions of several variables.

Example: $\frac{\partial u}{\partial x}(x, y) = 0$

(iii) Integro-differential Equations- A differential equation which involves both integrals and derivatives of a function is known as Integro-Differential Equation.

Example: $\frac{d}{dx}u(x) + \int_{x_0}^{x} f(t, u(t))dt = g(x, u(x)),\ \ \mathrm{u}(\mathrm{x}_0) = \mathrm{u}_0,\quad \mathrm{x}_0 \geq 0$

(iv) Delay Differential Equations- Delay differential equation (DDE) is defined as the evolution of the system at a certain time, T say, depends on the state of the system at an earlier time, T-t, say. It is different from ordinary differential equations (ODEs) where the derivatives depend only on the current value of the independent variable. The solution of DDEs thus requires knowledge of current state as well as the state of certain time previously.

Example: $\frac{d}{dt}x(t) = f(x(t), x(t-\tau))$

- The Few mathematical models are described below:

(i) Let G be excesses of concentration of glucose and I be the excesses of concentration of insulin at time t over the equilibrium values. Then the differential equations as follows:

$$\frac{dG}{dt} = -m_1 G - m_2 I + g(t), \qquad (1)$$

$$\frac{dI}{dt} = -m_3 I - m_4 G + i(t), \qquad (2)$$

where g is basal glucose concentration and i is basal insulin concentration and m_1, m_2, m_3 and $m_4 > 0$ for the following reasons:

(a) If there is excess glucose, it tends to disappear to the liver and to the tissues so that $m_1 > 0$.

(b) If there is excess insulin, it helps in metabolizing glucose for the tissues so that $m_2 > 0$.

(c) If there is excess insulin, it tends to disappear so that $m_3 > 0$.

(d) If there is excess glucose, pancreas are induced to secrete insulin so that $m_4 > 0$.

(ii) The non linear mathematical model is created and the parameters description

is as follows:

C : C(t) : percentage of uncontrolled diabetic patients

D : D(t) : percentage of controlled diabetic patients.

I : Incidence of Diabetes Mellitus (constant){no. of cases diagnosed in time t & assumed that they have controlled diabetes}.

μ : Natural Mortality Rate.

λ : Probability of Diabetic person developing uncontrolled diabetes.

γ : Rate at which uncontrolled diabetes are cured.

ν : The rate at which diabetics patients with uncontrolled diabetes becomes severely disabled.

δ : The mortality Rate Due to uncontrolled diabetes.

Rate of Change is defined by ODE (Non linear mathematical model):

$$D'(t) = \frac{dD}{dt} = I - (\lambda + \mu)D + \gamma C \quad \text{.....(1)}$$

$$C'(t) = \frac{dC}{dt} = \lambda D - (\lambda + \mu + \nu + \delta)C \quad \text{.....(2)}$$

Equation (1) and (2) represent the mathematical model whose parameters are defined above.

(iii) Consider a mathematical model of glucose level G, glucose uptake activity X and insulin level I. Many parameters has been taken and on the basis of these parameters values a mathematical model is formed. This model includes the basal values also i.e. G_b and I_b.

The modal is defined as:

$$\frac{dG}{dt} = -m_1 G + m_2 I + m_1 G_b$$

$$\frac{dX}{dt} = -m_2 X + m_3 I - m_3 I_b + m_6 I_b$$

$$\frac{dI}{dt} = -m_3 I + m_4 G + m_4 m_5 - m_6 I + m_6 I_b$$

All the variables and parameters values used in mathematical models are described as:

G(t) : The plasma glucose concentration at time *t* (mg/dl)

X(t) : The generalized insulin variable for the remote compartment (min^{-1})

I(t) : The plasma insulin concentration at time *t* (μU/ml)

G_b : This is the basal preinjection value of plasma glucose (mg/dl)

I_b : This is the basal preinjection value of plasma insulin (μU/ml)

m_1 : Insulin independent rate constant of glucose rate uptake in muscles, liver and adipose tissue (min^{-1}).

m_2 : The rate of decrease in tissue glucose uptake ability (min^{-1}).

m_3 : The insulin independent increase in glucose uptake ability in tissue per unit of insulin concentration I_b (min^{-2}(μU/ml)).

m_4 **:** The rate of the pancreatic β-cell release of insulin after the glucose injection and with glucose concentration above h [(μU/ml)$min^{-2}$$(mg/dl)^{-1}$]

m_5 **:** The threshold value of glucose above which the pancreatic β-cells release insulin.

m_6 : The first order decay rate for insulin in plasma (min^{-1}) pancreatic β-cells release insulin.

6. Proposed / Expected Outcomes of the Research

(1) The expected research outcome of the proposed research work would be the making of new and advanced differential equation mathematical model for better result in the field of diabetes mellitus.

(2) In this work such kind of models will be developed which will use the minimum numbers of parameters and will able to control the number of Diabetic persons which is increasing day by day.. This can be done by using various factors affecting the diabetes mellitus which include Exercise, Diet, and Medicines etc.

(3) The study inculdes the application of some mathematical model in the field of diabetes mellitus using the differential equation and get an insight into the problem in this area.

(4) The population models will give an idea of the future that how many people will be suffering from diabetes so that proper medication and facilities can be provided and research can be done in this area to control the increasing diabetic population and hence it will be very helpful in the field of medical science and also an ordinary man can understand it in an easy manner through presentation.

Proposed Time Frame

Work / Time	1st Year		2nd Year		3rd Year		4th Year	
	Six months	Six months	Six months	Six months	Six months	Six months	Six months	Six months
Course work & Literature Survey	←	→						
Literature review and lab visit			←	→				
Analyzing parameters and creating models				←	→			
Analysis & Paper Writing					←	→		
Thesis Writing & Submission							←	→

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